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BUCCAL FILM: A NOVEL TECHNOLOGY FOR IMPROVING THE BIOAVAILABILITY

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ABSTRACT

Buccal film is an innovative form of film. The buccal drug delivery system is used to provide buccal film. Buccal film is a graceful and effective dose form that improves absorption by avoiding the hepatic first pass metabolism. It is more appropriate than other dose forms because it adheres to the buccal layer of the oral cavity in a suitable way. It is affordable, biodegradable, easy to grip, non-irritating, and does not require the patient to ingest the medication. Buccal film is a convenient dosage form that is tiny in size, dose, and easy to deliver. Solvent casting, hot melt extrusion, and direct milling are the main methods used to create buccal film formulation. Ingredients of buccal films are drug, film forming polymer, plasticizer, saliva stimulating agent, sweeting agent, flavouring agent, and surfactant. Buccal film is a pioneering dosage because of its wide use of advantages to elderly, paediatric as well as patients having swallowing issues. The application of buccal film includes cough, allergy, pain disorder and certain local oral disease condition can be treated by using drug in the form of buccal film. Buccal film is capable area for continued research with the goal of systematic delivery of orally inefficient drugs. It is alternative source for non-invasive delivery of strong peptide and protein drug molecules. Buccal film is buccoadhesive drug delivery system which enhances safety, efficacy and stability of active pharmaceutical ingredient. Buccal film is novel technology due to its superior option to improve therapeutic efficacy.

KEYWORDS: Buccal film, bioavailability, novel technology, Solvent casting.

INTRODUCTION

The current article focuses on buccoadhesive drug delivery methods, which adhere to mucus-covered biological surfaces. Research relating to patient comfort and compliance is increasingly in demand nowadays. The creation of buccal films, which disintegrate on the patient's buccal mucosa, is another unique technique. This drug delivery method is appropriate for medications with a high first pass metabolism and is used to increase bioavailability by lowering the frequency of dosage to approach plasma peak levels, which reduces the likelihood of negative side effects. Additionally, it makes elderly and paediatric patients cost-efficient and effective. Due to their compact design and thinner thickness, films have also increased patient compliance when compared, for instance, to lozenges and tablets.[1,2]

History of buccal drug delivery system

In 1947, dental adhesive powders for the application of mucoadhesive polymers were employed for the creation of pharmaceutical formulations in an effort to create a penicillin drug delivery system for transferring the bioactive agent to the oral mucosa utilising gum tragacanth. When petrolatum and carboxy methyl cellulose (CMC) were employed in the formulation development, promising results were reported. A mucoadhesive delivery vehicle consisting of finely powdered sodium CMC (SCMC), pectin, and gelatin was designed as a consequence of further study. Later, Orahesive^{R} was deployed to market the formulation. Orabase^{R}, a fusion of polymethylene with mineral oil base, is another formulation that has undergone clinical studies. The advent of a method that paired polyethylene sheet with a slurry of SCMC and polyisobutylene followed next, and it had the added benefit of shielding the mucoadhesive layer by the polyethylene backing from the physical interference of the surrounding environment. Throughout the years, other similar polymers have been recognized to exhibit mucoadhesive features, such as sodium alginate, SCMS, guar gum, hydroxy ethyl cellulose, karya gum, methyl cellulose, polyethylene glycol, and tragacanth. The development of formulations with mucoadhesive qualities involved extensive research into poly acrylic acid, hydroxypropyl cellulose, and SCMC in the 1980s. Since then, mucoadhesive formulations have become more and more

often developed using acrylate polymers. Many experts have explored at the mucoadhesive characteristics of various polymers with diverse molecular structures. [3-7]

Physiology of BDDS

The administration of the desired medicament through the buccal mucosal membrane lining of the mouth cavity is characterized as buccal drug delivery. Drug delivery through this route is efficacious for both mucosal (local influence) and transmucosal (systemic effect) consequences. Buccal drug administration bypasses the first pass hepatic processing and offers direct access to the systemic circulation through the jugular vein, resulting in excellent bioavailability. Others include easy withdrawal, painless administration, the ability to include permeation enhancers, enzyme inhibitors, or pH modifiers in the formulation, and flexibility in designing as multidirectional or unidirectional release systems for local or systemic action. Other benefits include excellent accessibility, low enzymatic activity, and suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa.[8]

Mechanism of buccal absorption

Drugs are absorbed through the buccal mucosa via passive diffusion of nonionized species across the epithelium's intercellular gaps, which is primarily controlled by a concentration gradient. The main transport mechanism is the passive movement of non-ionic species through the lipid membrane of the buccal cavity. Like many other mucosal membranes, the buccal mucosa has been described as a lipoidal barrier to the passage of medications; the more lipophilic the drug molecule, the easier it is to absorb. A first order rate process can accurately capture the kinetics of medication absorption in the mouth. There are a number of possible obstacles to buccal medication absorption.[9]

Potential benefits of buccal films

Due to their wide surface area and quick breakdown and dissolution in the mouth cavity, buccal films let API enter the bloodstream.

- There is no need to chew or swallow.
- There is no risk of choke.
- GI enzymes may be able to prevent drug breakdown.
- The drug will be safeguarded against an acidic environment.
- Buccal Films may be administered on one's own.[10]
- Ease of administration for paediatric and geriatric patients, as well as for individuals who are mentally handicapped, noncooperative, or have physical limitations.
- Bypassing the hepatic first pass metabolism, the film improves the medicines systemic bioavailability.
- Buccal Films offer a quick start to the action.
- Buccal Films have high structural stability.[11]
- It is possible to hide tastes.[12]
- Buccal films enhance the bioavailability by extending the dosage form's time in contact with the absorption site.
- Less likelihood of adverse consequences.
- Compared to liquid medication forms, buccal films offer accurate dosing.
- It is possible to disguise taste.
- Buccal films boost the bioavailability of the dose form by extending its stay at the absorption site.
- Buccal Films are simple to store and portable.
- More cost-effective.[13]

Disadvantages

- It is not advisable to use medications that are unstable at buccal pH.
- The buccal membrane has low permeability.
- It is not appropriate for high dosages.
- Unpleasant-tasting and odorous drugs should not be used.
- Restrictive absorption space.
- Constant salivation demonstrates medication dilution.
- Restrictions on eating and drinking are possible.
- This approach can only be used to give medications that are absorbed by passive diffusion.
- Generally, not appropriate for youngsters.
- In sick circumstances, often unsuitable.[14]

MATERIALS AND METHODS

Drug Substance

Based on pharmacokinetic characteristics, the drug substance employed in the buccal drug delivery method should be chosen. The drug substance has to exhibit the qualities listed below.

- The drug's Standard Single Dose need to be modest.
- The pharmacological substance's biological half-life must be between 2 and 8 hours.
- The drug's Tmax should exhibit wide changes when taken orally.
- Passive absorption should occur when the medication is taken orally.
- The medicine should have a first-pass impact when taken orally.[15]

Polymers

The qualities listed below should be included in a perfect bio adhesive polymer for buccal drug delivery systems:

- It should be inert
- It should be adaptable to biological membrane
- It should be harmless
- It should form strong non covalent bond with mucin
- It should have high molecular weight
- It should have narrow distribution
- It should not decompose during half-life of the dosage form
- It must possess site specificity
- It should be economical
- It should be easily obtainable in the market. [16,17,18]

Diluents

For direct compression, lactose DC is used as the diluent due to its high-water solubility, flavouring qualities, and physico-mechanical features. Microcrystalline starch and starch are another illustration.[19]

Plasticizers

It is a component that the oral films must include. The choice of plasticizer is influenced by the polymer's compatibility as well as the type of solvent employed in the casting of the film. It lessens the brittleness of the film and increases its flexibility. They are utilised in concentrations ranging from 1 to 20% by weight of dry polymer. Glycerol, propylene glycol, low molecular weight polyethylene glycols, citrate derivatives such as triacetin and acetyl citrate, phthalate derivatives such as dimethyl, diethyl, and dibutyl derivatives, castor oil, etc. are a few examples.[20]

Sweeting agents

Sweetening compounds are essential in all food and medicinal preparations that break down or dissolve in the mouth. Sucrose, dextrose, fructose, glucose, liquid glucose, and maltose are the typical sources of sweetener. In comparison to sucrose and dextrose, the tongue quickly accepts the sweetness of fructose. However, using natural sweeteners poses a serious problem for diabetes individuals. Artificial sweeteners are increasingly widely used in food and medicinal preparations as a result. The first generation of artificial sweeteners includes saccharin, cyclamate, and aspartame, while the second generation includes acesulfame-K, sucralose, alitame, and neotame.[21,22]

Flavouring agents

It has been found that flavouring agents significantly influence how much people like a food. For the purpose of choosing a flavouring ingredient, synthetic flavour oils, oleo resins, and extract from various plant components such as leaves, fruits, and flowers are employed. The amount of flavouring ingredient required to disguise taste depends on the intensity of the flavouring agent.

Colouring agents

When some of the formulation components or medications are present in insoluble or suspension form, pigments like titanium dioxide or FD&C approved colourants are used (not exceeding concentration levels of 1%w/w) in buccal film formulation.

Stabilizing and thickening agents

To increase the viscosity and consistency of the dispersion or solution of the film preparation before casting, stabilising and thickening agents must be added. Examples of natural stabilisers and thickeners include xanthan gum, locust bean gum, carrageenan, and cellulose derivatives. They are utilised in concentrations as high as 5%w/w. [23]

Manufacturing methods of buccal film

The following three procedures are primarily used to create buccal film formulation.

1. **Solvent casting method:** In the solvent casting process, the necessary amount of polymer is introduced and dissolved in distilled water. This solution contains a tiny amount of an active medicinal component. Plasticizer is added into the solution and well mixed. After that, the solution is cast onto a baking plate and dried in a hot air oven at 400C. Once it had dried, cut it out of the petri dish with a knife, and then leave it in the desiccator for 24 hours. From this point on, cut to the desired size and form.
   Solvent Casting Method Steps
   Step 1: Prepare the casting solution
   Step 2: Deaeration of the solution
   Step 3: Pour the proper amount of solution into the mould
   Step 4: Drying the casting solution cut the finished dosage form to the required size in step 5 to add the desired amount of medication. [24,25]
2. **Hot melt extrusion method:** The medication and other excipients are melted together when using the hot melt extrusion process. The material is then pressed through an aperture to produce a more homogeneous product in a variety of forms, such as granules, tablets, or films. Transdermal medication delivery systems employ it.
   Steps in the Hot Melt Extrusion Method
   Step 1: The medication is combined with solid carriers.
   Step 2: A heated extruder melts the mixture.
   Step 3: Using dies, the melted substance is finally moulded into films.
3. **Direct milling method:** This procedure uses no solvents. Using either direct grinding or kneading, the medicine and excipients are combined in this manner without the use of fluids. The finished product is then rolled onto a release liner until the desired thickness is achieved. Because there is little chance of leftover solvent and no relationship with solvent-related health issues, this approach is often preferred.[26]

EVALUATION TESTS

Thickness uniformity

The thickness of several film formulations was assessed using thickness gauges with a minimum count of 0.01mm. By measuring the thickness of three films at three separate locations, the average film thickness was computed.

Weight variation

Five films with comparable specifications were picked from each formulation and put through a weight variation test using a Schimadzu digital scale in accordance with IP procedure. The weight of each buccal film was deducted from the average weight of five

buccal films. For each formulation, mean and SD values were computed.[27]

Percentage swelling index

On a cover slip that had already been pre-weighed, a medication in loaded 2 x 2 cm film was weighed. It was maintained in a Petri plate, to which 50 cc of phosphate buffer at pH 6.8 was added. The cover slip was taken off after every 5 minutes and weighed for up to 30 minutes. Due to film swelling with water absorption, the weight difference results in an increase in weight. The equation below was used to get percent swelling, % SI.[28]

Percent swelling (% SI) = $(X_t\text{-}X_0/X_0) \times 100$

Where, Xt = weight of the swollen film after time t

X0 = initial film weight at time zero.

Drug content uniformity

2 x 2 cm 2 films were held in 25 ml of phosphate buffer pH of 6.8. After being sonicated for five minutes, this solution was filtered. After the proper dilutions the drug concentration was measured spectroscopically using a UV visible spectrophotometer at 353 nm.[29]

Surface pH

The buccal film's surface pH should be kept as near to neutral as feasible since an acidic or alkaline pH may irritate the oral mucosa. For this, a mixed pH electrode is employed. pH was determined by placing the electrode in contact with the surface of the oral film after it had been briefly wetted with water.[30]

% Moisture loss

Accurately weighed buccal films, placed in a desiccator with anhydrous calcium chloride. The films were removed after three days and weighed. The following calculation was used to determine the % moisture loss:

SI (%) = $W_2\text{-}W_1/W_1 \times 100$

Moisture loss (%) = Initial weight -Final weight / Initial weight × 100

% Moisture absorption

The buccal films were precisely weighed and put in desiccators with 100ml of saturated aluminium chloride solution while ensuring 76% and 86% RH. The films were removed and weighed three days later.[31]

Folding endurance

For the finished films, the folding endurance was manually measured. An approximately 2 x 2 cm 2 strip of film was cut, and it was periodically folded until it broke. The value of folding endurance was determined by how many times the film could be folded in the same area without breaking.

Mucoadhesion time

After adhering the films to recently sliced buccal mucosa, the mucoadhesion time was measured. Araldite was used to adhere the buccal mucosa to the glass slide, and the films were applied to the mucosa before being softly squeezed with the fingertips. Place this glass slide in a 500 ml beaker with a slant and fill with the prepared phosphate buffer (pH 6.8) until the film is submerged. Put this beaker on the magnetic stirrer (remi) at 150 revolutions per minute. The mucoadhesion time was measured as the length of time it took for the film to separate from the buccal mucosa.[32]

Drug release

The produced formulations were fixed to glass slides using araldite before the piroxicam buccal films were analysed using the Dissolution Test Apparatus-IP Paddle (Electro Lab Bombay, India). The beakers were filled with 250 ml of pH 6.8 phosphate buffer and the glass slides. The apparatus's temperature and rotational speed were maintained at 37°F (0.5°C) and 50 rpm throughout the release research. The release research took place for 8 hours. Samples were taken out and replaced with new medium every hour. At 353 nm, samples were examined for piroxicam using a UV-visible spectrophotometer (UV-1800, Shimadzu).[33]

THERAPEUTIC APPLICATIONS OF MUCOADHESIVE BUCCAL FILMS

Anti-viral: To assess the pharmacokinetic profile of acyclovir when delivered from mucoadhesive buccal films, in vivo examinations were executed on rabbits. In vivo research indicate that buccal films surpassed oral solution in terms of absorption (Cmax 360.93 ng/mL; P0.0001), duration (Tmax 6 h), and AUC0- (5 folds, P0.0001) (control).[34]

Anti-fungal: The medication Miconazole and urea were used in increasing concentrations to produce buccal bioadhesive films. Microbiological analysis of all manufactured films revealed that, in a concentration-dependent manner, films containing increasing concentrations of both miconazole and urea had larger inhibitory zone widths (30–40 mm) than films containing miconazole alone (18 mm).[35]

Cardiovascular: With a biological half-life of roughly 2 hours, ivabradine hydrochloride is an anti-anginal medication. A blend of Carbopol 940, PEG 6000, and the two HPMC K15M and K100M extended the release up to 6 hours.[36]

Diuretics: Amiloride hydrochloride is a potassium-saving diuretic and antihypertensive medication that works by blocking the Na+ channels at luminal site When in-vitro and in-vivo profiles were compared, a good correlation was found that demonstrated the formula that replicates the in vitro release pattern across the biological membrane.[37]

Analgesic: A synthetic opioid analgesic that works centrally and binds to particular opioid receptors is tramadol hydrochloride. It is indicated as a first-line medication for the treatment of acute pain brought on by orthopaedic or surgical injuries, as well as for the

management of chronic pain. Films provided regulated release for more than 10 hours without causing mucosal irritation.[38]

Anti-depressant: Serotonin reuptake is specifically inhibited by dapoxetine hydrochloride. It prevents the absorption of serotonin by neurons and the resultant potentiation of the pre- and post-synaptic receptors for neurotransmitters. The bioavailability of dapoxetine hydrochloride is around 42%, which is relatively low. Dapoxetine hydrochloride was created as buccal films to increase its bioavailability and inhibit hepatic first-pass metabolism.[39]

Cancer: Using HPC as a polymer matrix and PEG 400 as a plasticizer, buccal films were developed as bioadhesive oral films that are packed with U. barbata dry ethanol extract. These results support the use of UBE-laden bioadhesive oral films as in treatment and prevention of oral cancer.[40]

Migraine: Rizatriptan benzoate, which acts more quickly than other medications, can be used to treat it. Because of hepatic metabolism, rizatriptan benzoate can be absorbed and demonstrate bioavailability at around 45% after oral ingestion.[41]

Parkinson's disease: Selegiline for the early management of Parkinson's disease, buccal films are prescribed because they might attach to the buccal mucosa and increase medication absorption via it. It extends medication release and improves bioavailability.[42]

Table no-:1 Previous research works on buccal films.

Sr. No.	Title of the report	Method	Polymers used	Reference
01	Ex vivo evaluation of bioadhesive films for buccal delivery of fentanyl	Solvent casting method	PVP K30, PVP K90 and ammonio methacrylate	[43]
02	Physicochemical Characterization and Evaluation of Buccal Adhesive Patches Containing Propranolol Hydrochloride	Solvent casting method	Chitosan, PVP k30.	[44]
03	Design and characterization of chitosan-containing mucoadhesive buccal patches of propranolol hydrochloride	Solvent casting method	Chitosan, PVP K30.	[45]
04	Mucoadhesive Bilayered Patches for Administration of Sumatriptan Succinate	Solvent casting method	Chitosan, gelatin, ethyl cellulose and PVP K30	[46]
05	Formulation, development and in vitro evaluation of mucoadhesive buccal patches of methotrexate	Solvent casting method	Sodium alginate, sodium C.M.S., PVP, ethyl cellulose and carbopol934	[47]
06	Formulation and evaluation of rabeprazole buccal patches	Solvent casting method	HPMC, PVP and gelatin.	[48]
07	Formulation of unidirectional release buccal patches of carbamazepine and study of permeation through porcine buccal mucosa.	Solvent casting method	HPMC K15M, PVA, EC, and PVP K30	[49]
08	Formulation and evaluation of chitosan containing mucoadhesive buccal patches of metoprolol succinate	Solvent casting method	Chitosan, PVP K30.	[50]
09	Formulation and evaluation of mucoadhesive buccal patches of aceclofenac	solvent casting method	PVP K30, HPMC, PVA, Carbopol 934-p and Eudragit L-100	[51]
10	Development of Mucoadhesive Buccal patch containing Aceclofenac: In vitro evaluations	solvent casting method	PVA, Gelatin and poly-sodium CMC	[52]
11	Preparation and evaluation of mucoadhesive buccal films of clotrimazole for oral candida infections	solvent casting method	Sodium CMC, Carbopol 974-p	[53]
12	Evaluation of laminated muco-adhesive patches for buccal drug delivery	solvent casting method	hydroxyethyl cellulose, hydroxypropyl cellulose, poly(vinylpyrrolidone) and poly (vinyl alcohol)	[54]
13	Bioadhesive polymer buccal patches for buprenorphine-controlled delivery: formulation, in vitro adhesion and release properties, Drug Dev	two-roll milling method	polyisobutylene, polyisoprene, and Carbopol 934P	[55]
14	Transmucosal delivery of domperidone from bilayered buccal patches: in vitro, ex vivo and in vivo characterization	solvent casting technique	HPMC E-15, PVP K-30	[56]
15	Development and characterization of Eudragit based mucoadhesive buccal patches of salbutamol sulfate	solvent casting technique	Eudragit L-100, HPMC, PVA and Carbopol 934	[57]

Table no-2: Patents on buccal films.[58]

Sr. No.	Title	Inventors	Patent number
01	Orally administrable films and preparation thereof	Meir haber, Throdis Kristmundsdottir, Skuli Skulason	US8840935B2
02	Dissolvable tobacco film strips and method of making the same	Wern et al	7946296B2
03	Two phase mucoadhesive composition	Richard C Fuisz	US20070298087A1
04	Water soluble film for oral administration with instant wettability	Zerbe et al	5948430
05	Transmucosal delivery of proton pump inhibitor	Kenneth Widder, Warren Hall, Kay Olmstead	US20040006111A1
06	Thin film strips	Berry et al	7241411
07	Film bandage for mucosal administration of actives	James E Biegasjskji	US20070172515A1

Table no-:3 Marketed preparations for BDDS.[59]

Sr. No.	Product	Manufacturer	Purpose
1.	Orajel	Del	Mouth freshner
2.	Setofilm	Bioalliancepharma	Prevention of nausea and vomiting
3.	Triaminic	Novartis	Antiallergic
4.	Donepezil rapid film	Labtec	Alzheimer's disease
5.	Chloraseptic	Prestige	Sore throat
6.	Klonopin wafer	Solvay pharmaceuticals	Treatment of anxiety
7.	Benadryl	Pfizer	Antiallergic

CONCLUSION

According to the present review, buccal film is the best dosage form. Buccal films offer a wide range of benefits to people of all ages. Hydrophilic polymer that dissolves quickly on the tongue or buccal cavity is used to create buccal film. The buccal film enhances absorption while avoiding first pass metabolism and also enhance bioavailability. Buccal film gives rapid onset of action. Buccal film improves the safety, efficacy, stability of the drug. Buccal film has good buccoadhesive property. It is novel technology due to its improved option to optimize therapeutic efficacy.

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